

The Association of Blood Lead Level and Cancer Mortality among Whites in the United States

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Lead is classified as a possible carcinogen in humans. We studied the relationship of blood lead level and all cancer mortality in the general population of the United States using data from the National Health and Nutrition Examination Survey II (NHANES II) Mortality Study, 1992, consisting of a total of 203 cancer deaths (117 men and 86 women) among 3,592 whites (1,702 men and 1,890 women) with average of 13.3 years of follow-up. We used Cox proportional hazard regression models to estimate the dose-response relationship between blood lead and all cancer mortality. Log-transformed blood lead was either categorized into quartiles or treated as a continuous variable in a cubic regression spline. Relative risks (RRs) were estimated for site-specific cancers by categorizing lead above and below the median. Among men and women combined, dose-response relationship between quartile of blood lead and all cancer mortality was not significant ($p_{\text{trend}} = 0.16$), with RRs of 1.24 [95% percent confidence interval (CI), 0.66–2.33], 1.33 (95% CI, 0.57–3.09), and 1.50 (95% CI, 0.75–3.01) for the second, third, and fourth quartiles, respectively, compared with the first quartile. Spline analyses found no dose response ($p = 0.29$), and none of the site-specific cancer RRs were significant. Among men, no significant dose-response relationships were found for quartile or spline analyses ($p_{\text{trend}} = 0.57$ and $p = 0.38$, respectively). Among women, no dose-response relationship was found for quartile analysis ($p_{\text{trend}} = 0.22$). However, the spline dose-response results were significant ($p = 0.001$), showing a threshold effect at the 94th percentile of blood lead or a lead concentration of 24 $\mu\text{g}/\text{dL}$, with an RR of 2.4 (95% CI, 1.1–5.2) compared with the risk at 12.5 percentile. Because the dose-response relationship found in women was not found in men, occurred at only the highest levels of lead, and has no clear biologic explanation, further replication of this relationship is needed before it can be considered believable. In conclusion, individuals with blood lead levels in the range of NHANES II do not appear to have increased risk of cancer mortality. **Key words:** cancer, lead, mortality, NHANES II, United States. *Environ Health Perspect* 110:325–329 (2002). [Online 28 February 2002] <http://ehpnet1.niehs.nih.gov/docs/2002/110p325-329/jemal/abstract.html>

Lead is an established carcinogen in experimental animals (1,2). Administration of inorganic lead to rats and mice by different routes resulted in development of renal tumors, gliomas, and/or lung adenomas. In contrast, lead is classified as a possible carcinogen in humans. Results of epidemiologic studies investigating the association of lead exposures with cancer are inconsistent and vary according to the type of cancers reported. For example, although Wong and Harris (3) reported a non-significant mortality deficit for kidney cancer [standardized mortality ratio (SMR) = 63.6; 95% confidence interval (CI), 33.9–108.7], Steenland et al. (4) reported an excess risk (SMR = 240; 95% CI, 103–471), especially in the high-lead exposure group. Steenland and Boffetta (5) summarized the results of the preceding two epidemiologic studies and six others in cohorts of lead smelter and battery workers exposed decades ago. They concluded that there was only weak evidence associating lead with cancer; lung cancer, stomach cancer, and gliomas were the most likely candidates.

Many of the epidemiologic studies that relate lead with cancer are in occupational

settings. To our knowledge, no study has examined the association between lead and cancer in the general population. In this paper, we present the results of our investigation of the association between blood lead levels and cancer mortality among whites in the general population of the United States using data from the National Health and Nutrition Examination Survey II Mortality Study, 1992 (NH2MS). Our analysis is restricted to whites because both blood lead concentrations (6) and cancer deaths (7,8) vary by race, and the number of deaths in blacks and other races in NH2MS were too small to provide reliable estimates.

Materials and Methods

The National Health and Nutrition Examination Survey II (NHANES II) was conducted between 1976 and 1980 to collect data from a national probability sample of the U.S. civilian, noninstitutionalized population, 6 months to 74 years of age, a total of 27,801 persons (9). The survey included standardized questionnaires, physical examinations, and laboratory tests. Blood samples

for lead measurements were drawn from all children < 7 years of age and from a random subsample of one-half of the persons \geq 7 years of age. The NH2MS is a passively followed mortality study of the NHANES II participants (10) designed to examine the association between factors measured at baseline and overall or cause-specific mortality.

The NH2MS included 9,252 participants (87.5% whites, 8,091/9,252) who were \geq 30 years of age at the time of their NHANES II examination and whose vital status was ascertained after 12–16 years by searching the National Death Index (National Center for Health Statistics, Hyattsville, MD) and the Social Security Administration Death Master File (11). As of 31 December 1992, 23.3% of the white participants (1,887/8,091) were deceased. Blood lead had been measured in a random subsample consisting of 46.3% (3,748/8,091) of whites, which forms the study sample for our analyses; 22.3% (836/3,748) of this subsample died, with the underlying cause of death specified for 817 deaths and unspecified for 19 deaths according to *International Classification of Diseases, Revision 9 (ICD-9) code (12)*. Deaths with unknown underlying cause were excluded from analyses. We also excluded from analyses a single participant who was lost to follow-up and 136 participants (equal numbers of men and women) with missing data for one or more of the covariates used during analyses. The total number of participants used in the final analyses was 3,592 (1,702 men and 1,890 women). The analytic cohort was restricted to whites.

The exposure variable of interest, lead concentration (micrograms per deciliter) in blood samples measured at the NHANES II baseline, was determined by a modified microcup atomic-absorption method (6). Blood lead was used in the analyses as a continuous variable where it was (natural) log transformed, or it was categorized into either four groups, divided into sample-weighted quartiles for all study subjects (sample weights

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were provided on the public use file from the National Center for Health Statistics), or into two groups, divided at the sample-weighted median. The log transformation was used to adjust the lead levels for skewness. The following confounding covariates were used as continuous or discrete variables at different stages of analyses. Age at baseline, rounded to the nearest year, was used as a continuous variable. Smoking was categorized as never, former, current < 1 pack, or current \geq 1 pack. Poverty index was used as a continuous variable determined by the Poverty Income Ratio as defined by the U.S. Bureau of the Census (Suitland, MD), a ratio of the total income of the household to a multiple of the total income necessary to maintain a family with given characteristics on a nutritionally adequate food plan (13). Alcohol consumption was used as a continuous variable and was obtained by summing the number of times alcoholic beverages (beer, liquor, and wine) were consumed per week. Region of residence was recorded as Northeast, Midwest, West, or South. Examination year was categorized by year of the baseline survey except for the last two examination years (1979 and 1980), which were grouped into one category because of the small number of examinations in 1980. Examination year was used as a stratifying variable because of changing blood lead concentrations over the baseline examination period (14).

We used Cox proportional hazard regression analysis (15) with baseline age at examination as the only covariate to obtain age-adjusted relative hazards [henceforth referred to as relative risks (RRs)] for all cancer mortality by quartile of lead. Cox regression was also used to estimate multivariate-adjusted

RRs for quartiles of lead, adjusting for confounding covariates (16) that included age at examination, cigarette smoking, poverty index, alcohol consumption, region of residence, year of examination, and sex. For site-specific cancers, which were selected based on suggested or suspected associations reported previously (5,17), age-adjusted RRs and, for some cancers (lung, esophagus, kidney, and pancreas), age- and smoking-adjusted RRs were obtained from Cox regression analyses for blood lead levels above the (sex-combined) median compared with below the median. Lead was dichotomized above and below the median instead of categorized into quartiles because of small numbers of cases for each site-specific cancer.

Dose-response relationship of blood lead and all cancer mortality was analyzed in two ways: by testing for trend in the multivariate-adjusted RRs across the quartiles of lead and by modeling the log-transformed blood lead as a continuous variable using a 5-knot cubic regression spline (18) in the Cox regression analysis. For tests of trend for the RRs over the quartiles of blood lead, a linear term consisting of the median values for each quartile was placed in the Cox model instead of the dummy variables for the quartiles. The test for a dose-response relationship of lead using the spline was based on a Wald test (19).

For all Cox regression analyses, we designated the survival times (calendar time) for deceased individuals with all cancers or site-specific cancers as the underlying causes of death as event times, whereas the survival times for persons who were deceased from causes other than any form of cancer/site-specific cancers or not known dead at the end of the study period (31 December 1992)

were censored times. All analyses were done for both sexes combined and for men and women separately.

NHANES II has a complex sample design with multistage stratified cluster sampling and sample weighting of study participants (20). All analyses were performed using the software package SUDAAN, Release 7.5 (21) that takes into account the sample weights and the complexity of the sample design in the statistical modeling and inference (15). All significance tests were two-sided using 0.05 as the level of statistical significance.

Results

Table 1 presents selected characteristics at baseline for NH2MS whites by quartile category of blood lead measurement, showing possible correlates of blood lead level. All estimates in the table are weighted by the sample weights. Note that the sample sizes are not evenly distributed across the quartiles because the quartile categories were determined by the sample-weighted distribution of blood lead level and not by the unweighted distribution. The sample included more women (1,958) than men (1,770). For combined sexes and for each sex separately, smoking and alcohol consumption were higher with increasing blood lead level, blood lead levels were highest in the Northeast and lowest in the South, and blood lead level decreased over the course of the survey. Mean age decreased in men but increased in women with increasing blood lead level.

Table 2 presents age-adjusted only and multivariate-adjusted RRs of mortality from all cancer by quartile of lead, compared with the risk in the first quartile. The multivariate-adjusted RRs were smaller than

Table 1. Characteristics of the study cohort by sex and blood lead level.

Characteristics	Both sexes Quartiles of blood lead				Males Quartiles of blood lead				Females Quartiles of blood lead			
	1	2	3	4	1	2	3	4	1	2	3	4
Sample size	745	902	1,028	1,053	144	342	523	761	601	560	505	292
Person-years	9,752	11,776	13,060	13,480	1,751	4,212	6,365	9,655	8,002	7,564	6,695	3,825
Median blood lead ^a ($\mu\text{g}/\text{dL}$)	7.3	10.6	13.8	19.7	7.6	10.8	13.9	20.1	7.2	10.5	13.7	18.8
Age at baseline ^{a,b} (years)	48.3	49.3	49.9	49.6	50.8	48.9	48.9	48.6	47.8	49.2	50.9	52.3
Poverty index ratio ^{a,b}	2.6	2.9	3.1	2.9	2.7	3.1	3.2	2.9	2.6	2.7	3.0	2.9
Alcohol intake ^{a,b} (drinks/week)	1.2	2.2	2.7	4.4	1.8	2.9	3.4	5.2	1.0	1.8	2.0	2.5
Smoking at baseline ^a (%)												
Never	55.8	44.5	31.7	23.0	37.3	29.6	23.1	16.9	59.9	52.9	40.7	39.3
Former	21.5	24.0	29.2	28.4	42.0	37.2	40.5	33.1	16.9	16.5	17.3	15.5
< 1 pack/day	16.5	23.9	24.4	27.3	7.9	21.8	19.3	26.1	18.4	25.1	29.8	30.6
\geq 1 pack/day	6.3	7.6	14.7	21.3	12.8	11.3	17.1	23.8	4.8	5.4	12.2	14.7
Region ^a (%)												
Northeast	16.0	24.1	25.9	29.2	15.2	20.4	25.9	30.0	16.1	26.2	26.8	27.9
Midwest	21.8	22.2	24.8	26.4	17.8	21.4	24.0	25.4	22.7	22.7	25.5	28.9
South	39.2	25.5	22.0	18.4	44.5	26.0	25.9	18.7	38.0	25.3	17.9	17.7
West	23.0	28.2	27.4	26.1	22.4	32.2	25.2	26.3	23.1	25.9	29.8	25.5
Year of baseline exam ^a (%)												
1976	13.9	19.8	22.3	36.4	12.2	14.8	18.8	33.4	14.3	22.6	25.9	44.7
1977	21.3	24.0	23.3	26.8	23.6	20.4	23.5	27.1	20.8	26.0	23.2	26.2
1978	19.1	27.7	32.5	24.2	12.3	28.9	30.1	24.7	20.6	27.0	35.1	22.8
1979–1980	45.7	28.5	21.9	12.6	51.9	35.9	27.7	14.9	44.3	24.3	15.8	6.4

^aWeighted by sample weights from NHANES II. ^bMean value.

their corresponding age-adjusted RRs. Trends in the multivariate-adjusted RRs were not statistically significant for both sexes combined or for each sex separately.

Using Cox proportional hazard regression analysis and a 5-knot cubic regression spline to model the dose–response relationship

between log-transformed blood lead levels and all cancer mortality, we found a non-significant dose–response relationship among both sexes combined ($p = 0.17$) and among men only ($p = 0.38$). The spline results for men are displayed graphically in Figure 1. The confidence intervals are wide,

and there appears to be no statistically significant dose relationship. In contrast, there was a statistically significant dose–response association between blood lead level and cancer mortality among women ($p = 0.001$). When the spline results are displayed graphically (Figure 2), there appears to be a threshold effect of blood lead in women where the risk becomes significantly elevated after the 93rd lead percentile, which corresponds to a lead concentration of 24 $\mu\text{g}/\text{dL}$. This association is not apparent in the quartile analysis in Table 2 because the fourth quartile contains too broad a range of lead levels. However, if the fourth quartile is further subdivided into four subquartiles (17, 18–19, 20–23, and ≥ 24 $\mu\text{g}/\text{dL}$), the multivariate-adjusted RRs for these subquartiles are 0.72 (95% CI, 0.14–3.70) at the first subquartile, 0.53 (95% CI, 0.15–1.88) at the second subquartile, 1.44 (95% CI, 0.58–3.56) at the third subquartile, and 5.39 (95% CI, 2.19–13.24) at the fourth subquartile when compared with the first quartile; the increase in risk begins at the third subquartile, which is similar to the spline

Table 2. Sample-weighted and age-adjusted RRs for all cancer mortality by quartiles of blood lead level.

Sex/quartiles (blood lead, $\mu\text{g}/\text{dL}$)	No. of deaths	Age-adjusted		Multivariate-adjusted		p_{trend}
		RR ^a	95% CI	RR	95% CI	
Both sexes						
1 (≤ 9.8)	20	1.00	Referent	1.00	Referent	0.16
2 (9.9–12.9)	49	1.56	0.82–2.94	1.24	0.66–2.33	
3 (13.0–16.9)	64	1.81	0.82–4.01	1.33	0.57–3.09	
4 (≥ 17.0)	70	2.54	1.25–5.17	1.50	0.75–3.01	
Males						
1 (≤ 9.8)	4	1.00	Referent	1.00	Referent	0.57
2 (9.9–12.9)	24	2.19	0.69–6.95	2.00	0.63–6.33	
3 (13.0–16.9)	42	3.01	0.91–9.91	2.61	0.77–8.83	
4 (≥ 17.0)	47	2.99	0.92–9.69	2.02	0.63–6.46	
Females						
1 (≤ 9.8)	16	1.00	Referent	1.00	Referent	0.22
2 (9.9–12.9)	25	1.37	0.64–2.93	1.03	0.49–2.18	
3 (13.0–16.9)	22	1.22	0.44–3.35	0.77	0.29–2.10	
4 (≥ 17.0)	23	2.79	1.25–6.19	1.59	0.76–3.30	

^aRRs were not adjusted for confounding variables.

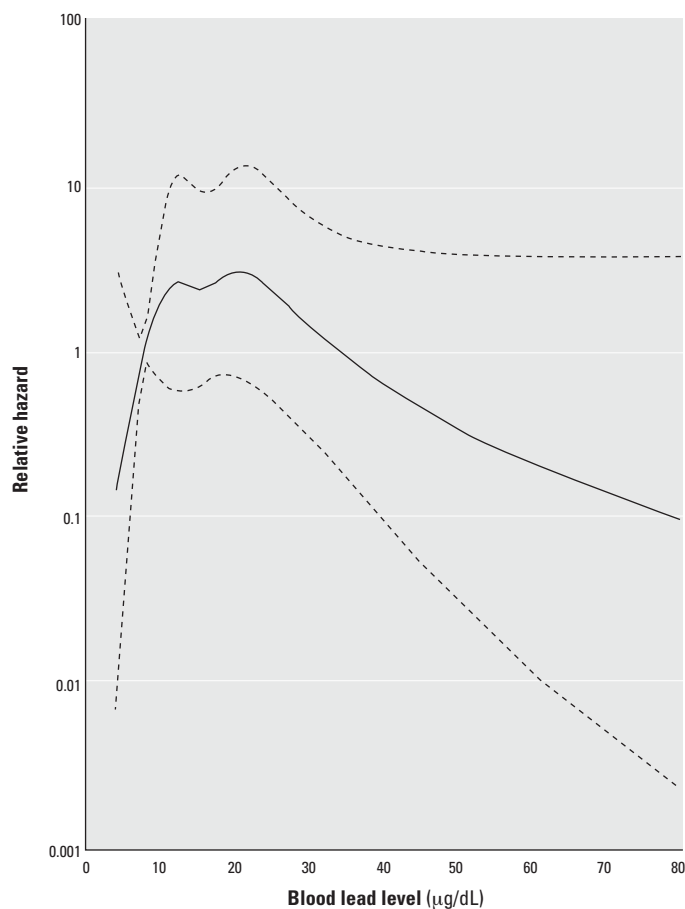


Figure 1. Relative risk of all cancer mortality for different blood lead levels compared with referent blood lead level of 8 $\mu\text{g}/\text{dL}$ (the 12.5th percentile) among white men in the United States (NHANES II). The solid line shows the fitted 5-knot spline relationship; the dashed lines are the pointwise upper and lower 95% confidence limits.

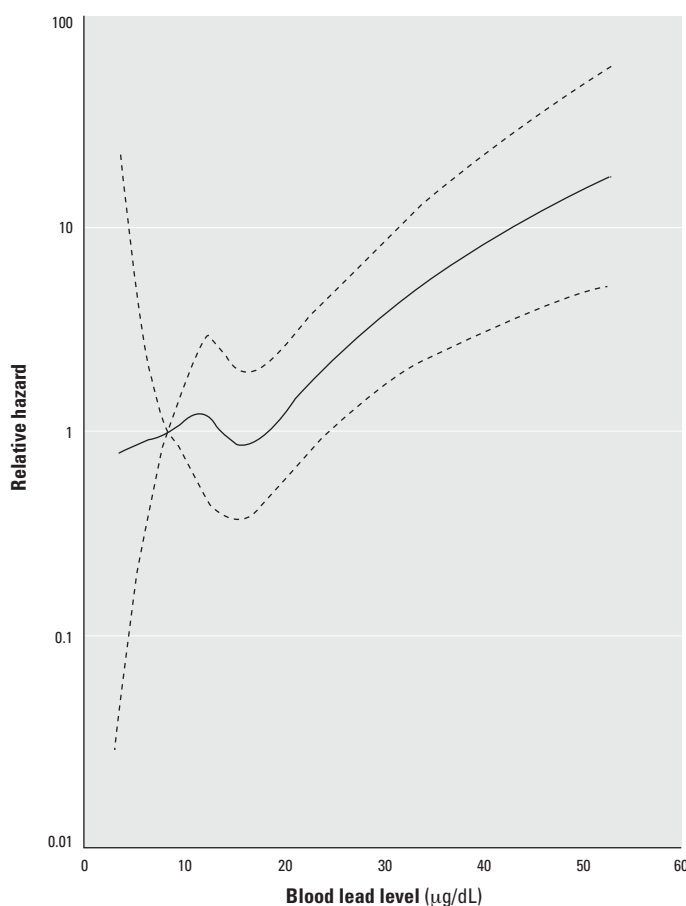


Figure 2. Relative risk of all cancer mortality for different blood lead levels compared with referent blood lead level of 8 $\mu\text{g}/\text{dL}$ (the 12.5th percentile) among white women in the United States (NHANES II). The solid line shows the fitted 5-knot spline relationship; the dashed lines are the pointwise upper and lower 95% confidence limits.

analysis. It should be noted that in the third and fourth subquartiles, there were only 7 and 10 cases, respectively, which indicates the relatively small sample sizes that drive these dose-response results. For the men only, we also subdivided the fourth quartile into four subquartiles (17–18, 19–20, 21–24, and ≥ 25 $\mu\text{g}/\text{dL}$) and estimated the multivariate-adjusted RR for these subquartiles as 1.42 (95% CI, 0.36–5.70) at the first subquartile, 2.15 (95% CI, 0.55–8.36) at the second subquartile, 3.5 (95% CI, 1.02–11.05) at the third subquartile, and 1.13 (95% CI, 0.21–6.24) at the fourth subquartile when compared with the first quartile. Although there is an increase in the third subquartile, there is no discernible dose response that agrees with the spline analysis.

A test for the proportional hazard assumption indicated that risks were constant over the follow-up period among both men and women combined ($p = 0.25$) and among men ($p = 0.54$), but were marginally significantly different ($p = 0.04$) among women. However, further evaluation of the relative risk for the first-half and second-half follow-up periods among women showed virtually similar relative risks. Also, the possibility of results being affected by individuals with self-reported cancer or with unreported or undiagnosed cancer at baseline was examined by excluding all participants with self-reported cancer or by excluding all deaths due to cancer within the first year of follow-up. The results were very similar to those from the full cohort (data not shown).

Table 3 presents the association of blood lead level with selected site-specific cancer mortality. None of the site-specific cancers showed a statistically significant excess risk. Among the combined sexes and among men, the risks increased for blood lead levels above the median except for prostate cancer among men and for brain cancer among both sexes combined. Among women, there was no clear pattern.

Discussion

In our analyses of the association of quartiles of blood lead concentrations with all cancer mortality in the white population of the United States, we found that the risk of cancer mortality was not significantly associated with blood lead level among men and women combined and among separate analyses of men and women. A statistically more powerful approach for determining a dose-response relationship is to treat blood lead as a continuous exposure using a 5-knot cubic regression spline in the Cox regressions (22). For both sexes combined and for men only, the spline analysis found no significant dose-response relationship, agreeing with the quartile analysis. However, for women

the spline analysis appears to show a threshold effect at about the 94th percentile of lead, corresponding to a blood concentration of 24 $\mu\text{g}/\text{dL}$. There was no strong evidence for an association of mortality from any of the selected site-specific cancers with blood lead level.

Whether lead causes cancer in humans is not well established (1,5). The site-specific cancers associated with lead exposure vary among epidemiologic studies. Steenland and Boffetta (5) did a meta-analysis of eight epidemiologic studies on cancer mortality or incidence among workers with high occupational lead exposure. They reported an increased risk for lung cancer (RR = 1.30; 95% CI, 1.15–1.46) and stomach cancer (RR = 1.34; 95% CI, 1.14–1.57), but they found little evidence of increased risk for kidney cancer (RR = 1.01; 95% CI, 0.72–1.42), brain cancer (RR = 1.06; 95% CI, 0.81–1.40), and all cancers combined (RR = 1.04; 95% CI, 1.00–1.09). Fu and Boffetta (17) performed a similar meta-analysis of published data using some of the studies common to the preceding meta-analysis, and found significant excess risk for all cancer, stomach cancer, lung cancer, and bladder cancer. Some of our results were in agreement with the summary results for all cancers by Fu and Boffetta (17). However, it is noteworthy that occupational lead exposure is much higher than environmental exposure. For

example, the mean blood lead levels of the occupational studies included in the above meta-analyses ranged from 26 $\mu\text{g}/\text{dL}$ to 80 $\mu\text{g}/\text{dL}$, compared with a weighted median blood lead level of 13 $\mu\text{g}/\text{dL}$ for our study population.

We have no ready explanation why there is an association of lead with mortality from all cancers for women in the highest lead levels but not for men, in view of the fact that lead levels are higher among men than among women across all age groups in the United States (6). It has been suggested that hereditary factors possibly related to lead uptake and storage play a major role in determining the concentration of lead in blood, especially in women (23). One may speculate that there could also be a hereditary/genetic factor that makes women more susceptible to the role of lead in carcinogenesis.

Blood lead levels have significantly declined over time in the United States (24), mainly due to removal of lead from gasoline and soldered cans. Mean blood lead values in the general population of the United States decreased from 12.8 $\mu\text{g}/\text{dL}$ in 1976–1980 (NHANES II) to 2.8 $\mu\text{g}/\text{dL}$ in 1988–1991 (Phase 1 of NHANES III). However, blood lead is still elevated among minority children. In 1991–1994 (Phase 2 of NHANES III), blood lead levels of ≥ 10 $\mu\text{g}/\text{dL}$ exceeded the maximum permissible concentration established by the Centers for

Table 3. Relative risks for selected site-specific malignant neoplasms among whites with blood lead measurement at baseline, using the risk of cancer mortality in the lower 50th lead percentile as a reference.

Sex/anatomic site (ICD-9 code)	Deaths	RR ^a	95% CI	p-Value
Both sexes combined				
Esophagus (150)	7	3.7	0.2–89	0.39
Stomach (151)	5	2.4	0.3–19.1	0.40
Colon and rectum (153–154)	16	1.2	0.4–3.7	0.79
Pancreas (157)	12	3.6	0.6–19.8	0.14
Trachea, bronchus, and lung (162)	71	1.5	0.7–2.9	0.29
Breast (174)				
Prostate (185)				
Kidney (189)	7	1.1	0.2–5.1	0.91
Brain (191)	5	0.5	0.1–5.8	0.60
Men				
Esophagus (150) ^b	5			
Stomach (151)	4	3.1	0.3–37.4	0.37
Colon and rectum (153–154)	6	2.2	0.3–15.8	0.44
Pancreas (157)	6	3.5	0.4–32.5	0.26
Trachea, bronchus, and lung (162)	52	1.2	0.6–2.5	0.66
Prostate (185)	11	0.6	0.2–2.2	0.46
Kidney (189)	5	3.2	0.4–27.7	0.28
Brain (191)	1			
Women				
Esophagus (150)	2			
Stomach (151)	1			
Colon and rectum (153–154)	10	0.8	0.2–3.9	0.83
Pancreas (157)	6	3.8	0.3–40.1	0.27
Trachea, bronchus, and lung (162)	19	2.5	0.7–8.4	0.14
Breast (174)	13	1.0	0.3–3.2	0.97
Kidney (189)	2			
Brain (191)	4	0.7	0.1–6.8	0.73

^aRelative risk from Cox proportional hazard regressions adjusted for age at examination for each site-specific cancer site and for smoking for esophagus, pancreas, lung, and kidney cancers. ^bNo deaths in the lower 50th lead percentile to estimate RR.

Diseases Control (25) in 11.2% of non-Hispanic black children ≤ 5 years of age (26). Although the public health importance of lead is declining in developed countries, it is dramatically increasing in developing countries (27–29). For example, over 90% of mixed race children in inner-city Cape Town, South Africa, have blood lead levels ≥ 10 $\mu\text{g}/\text{dL}$ (30). In addition to lack of awareness, policies, and regulations, reasons for the rise of blood lead levels in developing countries include increased exports of leaded gasoline to these countries in search of new markets as leaded gasoline is phased out in developed countries (28,31).

It is important to point out the limitations in the database and analyses used for our study. First, the NH2MS study is based on a passive follow-up whereby persons not found to be deceased were assumed alive. Thus, there is a potential for misclassification of vital status. Comparison of the survival of the NH2MS cohort to that of the U.S. population during the same time period to assess how well mortality was ascertained in the NH2MS study showed that cumulative survival probabilities for the NH2MS cohort were generally higher than expected probabilities calculated from the U.S. life table data (10); however, the differences were very small among whites. Second, lead level was based on a one-time measurement that could have random measurement error and could attenuate the estimated associations. In addition, this measurement may not accurately reflect cumulative exposure to lead but may only provide an approximation to it. This is a particularly important point given the apparent large decline in blood lead concentration in the U.S. population over the course of the survey because of increased use of unleaded gasoline. Ideally, we would need repeated measurements before and after baseline to more accurately measure cumulative lead exposure. Finally, the statistical power of this study is limited by the relatively small cohort size and follow-up time; as shown in Table 3, the number of deaths for site-specific cancers are too small to likely detect expected association with blood lead. If the National Center for Health Statistics performs future follow-ups of this important cohort, the increase in

the number of cancer deaths will enlarge the power of this cohort for detecting associations between blood lead and some of the more common cancers. Also, because this is a general population study, the blood lead levels in this study are lower than would likely be found among occupationally exposed populations; this further reduces the statistical power. These limitations in the size and exposure of this study sample may account for some of the statistically insignificant associations that were found.

The apparent dose–response relationship found only in women for the highest levels of lead could be a chance finding or could be due to residual or unmeasured confounding. Because the dose–response relationship found in women was not found in men, it occurred at only the highest levels of lead, and has no clear biologic explanation, further studies of populations with sufficiently high levels of lead exposure need to replicate our finding among women before it is believable. In conclusion, individuals with blood lead levels in the range of NHANES II do not appear to have increased risk of cancer mortality.

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